

92 PRIMARY GERM CELL TUMORS OF THE THORAX

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The biology and clinical characteristics of mediastinal germ cell tumors have been defined during the last 25 years. These neoplasms, although rare, are of particular interest because they predominantly affect young males and because curative therapy is now available for many patients. The clinical and pathologic characteristics of benign and malignant germ cell tumors and of "poorly differentiated carcinoma" of the mediastinum are presented, with special attention focused on the treatment of these neoplasms.

BENIGN TERATOMAS OF THE MEDIASTINUM

Benign teratomas of the mediastinum (mature cystic teratomas or "dermoid" tumors) are rare and account for only 3 to 12% of mediastinal tumors.^{1,2} Although these tumors have been described in patients with ages ranging from 7 months to 65 years, most occur in young adults, with an approximately equal incidence in males and females.^{2,4} No predisposing conditions or associated abnormalities have been recognized in patients developing these tumors.

Benign mediastinal teratomas have a histologic appearance identical to that of benign teratomas arising in the more common ovarian location. These tumors are usually well encapsulated and are composed either of a single large cystic cavity or of several smaller intercommunicating cystic spaces. On histologic examination, mature tissue from ectodermal, mesodermal, and endodermal germ cell layers is typically present. Mature tissue that recapitulates the histology of any human organ can be found in these tumors. However, the ectodermal component (i.e., skin, sebaceous tissue, neural tissue) is usually predominant.⁴

Approximately 95% of benign teratomas arise in the anterior mediastinum; the remainder arise in the posterior mediastinum.^{2,4} These tumors are slow growing, and in recent years, 50 to 60% of patients have been asymptomatic at the time of diagnosis by routine chest radiography.^{3,4} When symptoms are present, dyspnea and substernal chest pain are the most common. Cough productive of hair or sebum is pathognomonic of a benign mediastinal tumor. However, this distinctive symptom is extremely rare and occurs late in the natural history of this condition following tumor rupture into the tracheobronchial tree. Superior vena caval syndrome is also rare and is a late manifestation. Most patients with benign mediastinal teratomas appear healthy, and physical examination contributes little to the diagnosis. Likewise, laboratory evaluation is usually normal. Serum levels of human chorionic gonadotropin (hCG) and α -fetoprotein are always normal in patients with benign teratoma.

The chest radiograph typically reveals a well-circumscribed anterior mediastinal mass that often protrudes into one of the lung fields. These tumors are usually large at the time of diagnosis; in a recent series, the median size was 10 by 8.5 by 5.4 cm.⁴ Occasionally, chest radiography identifies teeth within the tumor, a pathognomonic finding. Calcification is present in up to 25% of tumors, occurring in fragments of bone, in the tumor wall, or in other areas throughout the tumor, in addition to its occasional occurrence in teeth.

Surgical excision is the treatment of choice for benign teratoma of the mediastinum. Median sternotomy is usually the best surgical approach, although successful resection can also be accomplished by thoracotomy. Surgical removal is sometimes difficult due to the large size of the tumor and the involvement of other structures: pericardium, lung, great vessels, thymus, chest wall, hilar structures, and diaphragm, in decreasing order of frequency. Some 10 to 15% of patients require additional procedures (e.g., lobectomy, pericardiectomy) for complete tumor resection. Benign teratomas are resistant to radiation and cytotoxic drugs, and these modalities have no role in their treatment.

Tumor recurrence is rare following complete surgical resection.^{2,4} Prolonged survival has also been reported in patients who underwent

only subtotal resection owing to the involvement of vital mediastinal structures. The operative mortality in recent years has been very low.

MALIGNANT GERM CELL TUMORS

ETIOLOGY Malignant mediastinal germ cell tumors of various histologies were first described as a clinical entity approximately 50 years ago.^{5,6} Mediastinal and other extragonadal germ cell tumors were initially thought to represent isolated metastases from an inapparent gonadal primary site. Anecdotal autopsy reports of occasional patients with small, unrecognized testicular primaries or fibrous scars (thought to represent sites of regressed primary tumors) supported this hypothesis.^{7,8} However, a large amount of evidence now substantiates the extragonadal origin of these neoplasms. Most patients with presumed extragonadal germ cell neoplasms have neither microscopic neoplasms nor fibrous scars identified at postmortem examination.^{9,10} In addition, a large autopsy series of patients with testicular germ cell cancer confirmed the rarity of isolated anterior mediastinal metastases, with this finding being present in less than 1% of patients.¹¹ Finally, large numbers of patients with mediastinal germ cell tumors are now long-term survivors, following either mediastinal irradiation for pure seminoma or combination chemotherapy for nonseminomatous tumors. Testicular recurrences have not been observed in these patients.

There is now general acceptance of the fact that extragonadal germ cell tumors, particularly in the mediastinal and pineal sites, represent a malignant transformation of germinal elements distributed to these sites and can occur in the absence of a primary focus in the gonad. Some investigators have suggested that this distribution arises as a consequence of abnormal migration of germ cells during embryogenesis.^{6,12} Others have hypothesized a widespread distribution of germ cells to multiple sites during normal embryogenesis, with these cells conveying genetic information or providing regulatory functions at somatic sites.¹³

INCIDENCE AND EPIDEMIOLOGY Malignant germ cell tumors of the mediastinum are uncommon, representing only 3 to 10% of tumors originating in the mediastinum.^{1,14,15} They are much less common than germinal tumors arising in the testes and account for only 1 to 5% of all germ cell neoplasms.^{16,17} These incidence figures, most of which are derived from retrospective series reported between 1950 and 1975, may underestimate the true incidence of mediastinal germ cell tumors. The histology of these tumors may be similar to that of other malignant mediastinal tumors, including malignant thymoma and high-grade non-Hodgkin's lymphoma. Some patients with "poorly differentiated neoplasm" or "poorly differentiated carcinoma" of the mediastinum have the i(12p) chromosomal abnormality diagnostic of germ cell tumor.^{18,19} Other patients with "poorly differentiated carcinoma" of the mediastinum have clinical characteristics and treatment responses typical of patients with extragonadal germ cell tumors.²⁰⁻²² Although there is no doubt that mediastinal germ cell tumors are uncommon, increasing familiarity with the tumors by both clinicians and pathologists will probably result in their increased recognition.

The great majority of mediastinal germ cell tumors occur in patients between 20 and 35 years of age. For unknown reasons, most are found in males. Approximately 25 cases have been reported in women, and these tumors seem histologically and biologically identical to those occurring in males. The relative rarity of extragonadal germ cell tumors in women parallels the lower incidence of female gonadal germ cell tumors as compared with their incidence in males.

Recent data suggest that the incidence of mediastinal germ cell tumors in racial minorities in the United States has increased, at least when compared with the very low incidence of testicular cancer among these minorities.^{23,24} In a recent American cooperative group experience, 7 of 45 patients (16%) with extragonadal germ cell tumors were from various racial minorities, as compared with 8 of 107 patients (7%) with primary testis tumors.²⁵

HISTOPATHOLOGY In general, mediastinal germ cell tumors appear histologically identical to germ cell tumors arising in the testis, and all histologic subtypes seen in testicular germ cell neoplasms have also been recognized in the mediastinum. In a recent review of 229 malignant mediastinal germ cell tumors seen between 1960 and 1994 at the Armed

Forces Institute of Pathology, pure seminoma was the most common histology, accounting for 52% of cases.²⁶ Nonseminomatous histologies included teratocarcinoma (20%), yolk-sac tumor (17%), choriocarcinoma (3.4%), embryonal carcinoma (2.6%), and mixed nonseminomatous tumors (5.2%).

CLINICAL CHARACTERISTICS Unlike benign germ cell tumors of the mediastinum, malignant mediastinal tumors are usually symptomatic at the time of diagnosis. Most malignant tumors are large and cause symptoms by compressing or invading local mediastinal structures, including the lungs, pleura, pericardium, and chest wall. Pure seminomas are somewhat slower growing and have less potential for early metastasis than do tumors with nonseminomatous elements; their initial presentation, therefore, varies somewhat. Pure seminomas and tumors with nonseminomatous elements are discussed separately, although a great deal of overlap exists in their clinical characteristics.

Seminoma. Seminomas grow relatively slowly and can become very large before causing symptoms. Tumors 20 to 30 cm in diameter can exist with minimal symptomatology. Some 20 to 30% are detected by routine chest radiography while still asymptomatic.²⁷ The most common initial symptom is a sensation of pressure or dull retrosternal chest pain. Additional symptoms include exertional dyspnea, cough, dysphagia, and hoarseness. Superior vena caval syndrome develops in approximately 10% of patients. Systemic symptoms related to metastatic lesions are uncommon.

At the time of diagnosis, only 30 to 40% of patients with mediastinal seminoma have localized disease, while the remainder have one or more sites of distant metastases.^{28,29} The lungs and other intrathoracic structures are the most common metastatic sites. The skeletal system is the most frequently involved extrathoracic metastatic site; the propensity of advanced testicular seminoma to metastasize to bone has also been recognized. The retroperitoneum is an uncommon site of metastasis in patients with mediastinal seminoma.^{10,28,30}

Pure seminoma appears radiographically as a large, noncalcified anterior mediastinal mass, which can compress or deviate the trachea or bronchi if of sufficient size. A computed tomography (CT) scan of the chest typically shows a large homogeneous anterior mediastinal mass that obliterates the fat planes surrounding mediastinal vascular structures.³¹ The radiographic findings are not specific enough to allow the distinction of mediastinal seminoma from other mediastinal tumors.

Elevated serum levels of hCG are detected in approximately 10% of mediastinal seminomas.²⁸ This incidence is similar to that reported in advanced testicular seminoma. Levels of hCG exceeding 100 ng/mL are unusual, and suggest the presence of nonseminomatous elements. The serum α -fetoprotein level is always normal in pure mediastinal seminoma, and any elevation of this tumor marker indicates the presence of nonseminomatous elements. Serum lactic dehydrogenase is also elevated in the majority of patients with mediastinal seminoma.²⁸

Nonseminomatous Germ Cell Tumor. Very few patients with these rapidly growing neoplasms are asymptomatic at diagnosis. Symptoms caused by compression or invasion of local mediastinal structures are identical to those seen in patients with mediastinal seminoma. However, presenting symptoms due to metastatic lesions are much more common, since 85 to 95% of these patients have at least one metastatic site at the time of diagnosis.³²⁻³⁵ Common metastatic sites include the lungs, pleura, lymph nodes (particularly supraclavicular and retroperitoneal), and liver. Less frequent sites of involvement include the bone, brain, and kidney. High levels of hCG sometimes are associated with gynecomastia. Neoplasms with elements of choriocarcinoma have a marked hemorrhagic tendency; these patients may have catastrophic events related to uncontrolled hemorrhage at a metastatic site (e.g., massive hemoptysis, intracranial hemorrhage).³⁵ Constitutional symptoms including weight loss, weakness, and fever are more common in these patients than in those with pure seminoma.

Chest radiographic features of mediastinal nonseminomatous germ cell tumors are similar to those seen in mediastinal seminomas. The CT scan frequently shows an inhomogeneous mass, with multiple areas of hemorrhage and necrosis, differing from the usually homogeneous appearance of mediastinal seminoma.³¹

The serum tumor markers hCG and α -fetoprotein are usually abnormal in patients with mediastinal nonseminomatous germ cell tumors. Alpha-fetoprotein is most frequently abnormal and is elevated either alone or in conjunction with hCG in approximately 80% of patients, whereas elevation of hCG occurs in only 30 to 35%.^{36,37} This pattern of marker elevation differs slightly from that seen in testicular cancer, where elevations of hCG and α -fetoprotein occur with nearly equal frequency and are seen in 50 to 70% of patients with metastatic tumor. As in mediastinal seminoma, elevation of serum lactic dehydrogenase is frequent, occurring in 80 to 90% of patients.³³

SYNDROMES ASSOCIATED WITH MEDIASTINAL NONSEMINOMATOUS GERM CELL TUMORS **Klinefelter's Syndrome.** Klinefelter's syndrome is a relatively common chromosomal abnormality characterized by hypogonadism, azoospermia, and elevated gonadotropin levels in association with an extra chromosome X. A slightly increased incidence of breast cancer has been described in these men, but a general predisposition to other cancers has not been observed.³⁸ The association of Klinefelter's syndrome and mediastinal nonseminomatous germ cell tumors is now well recognized.^{39,40} Four of 22 consecutive patients (18%) treated at Indiana University for primary mediastinal germ cell tumors had karyotypic confirmation of Klinefelter's syndrome, and an additional patient had clinical features.⁴¹ The average age of patients with Klinefelter's syndrome who develop extragonadal germ cell tumors is approximately 18 years, 10 years younger than the median age of those developing this tumor in the absence of Klinefelter's syndrome. Testicular germ cell neoplasms have rarely been reported in association with Klinefelter's syndrome; therefore, the association with mediastinal germ cell tumor seems specific.

The explanation for this association is unknown, but it seems reasonable to assume that the chromosomal abnormality plays some role. Increasing evidence indicates that many individuals who develop germ cell tumors have underlying germ cell defects. Many patients with extragonadal germ cell tumors have histories of infertility, and testicular biopsy in these patients shows various abnormalities, including decreased spermatogenesis, peritubular fibrosis, and interstitial edema.⁴² These data suggest that either a congenital or an acquired germ cell defect contributes not only to defective spermatogenesis but also to the development of extragonadal germ cell tumors.

Hematologic Neoplasia. A unique association between mediastinal nonseminomatous germ cell tumors and a variety of hematologic neoplasms is now well described. In one large series of patients with germ cell tumors, 3 of 34 patients with primary mediastinal germ cell tumors developed hematologic neoplasia, while none of 654 patients with testicular germ cell tumors developed such tumors.⁴³ Hematologic neoplasms have included acute myeloid leukemia, acute nonlymphocytic leukemia, acute lymphocytic leukemia, erythroleukemia, acute megakaryocytic leukemia, myelodysplastic syndrome, and malignant histiocytosis.^{28,43-48} In most patients, the hematologic neoplasia developed after the diagnosis of mediastinal germ cell tumor, but usually within 24 months. In several patients, the diagnoses of hematopoietic neoplasm and mediastinal germ cell tumor were simultaneous.

Recent evidence indicates that the hematologic neoplasms in this setting are not treatment related, but rather arise from clones of malignant lymphoblasts or myeloblasts contained within the mediastinal germ cell tumor. Foci of malignant lymphoblasts have been recognized histologically in several mediastinal germ cell tumors.^{49,50} More importantly, several patients have had an identical chromosomal abnormality (an isochromosome of the short arm of chromosome 12) in the neoplastic cells from the mediastinal germ cell tumor and the hematologic neoplasm, providing strong evidence for a common origin.⁵⁰⁻⁵² This karyotypic abnormality is a specific cytogenetic marker of extragonadal and testicular germ cell tumors.⁵³

These clinical observations are consistent with *in vitro* data, in which murine teratocarcinoma cell lines can be shown to differentiate into erythroid, myeloid, and megakaryocytic elements.^{54,55} The specific association of leukemias and other hematologic neoplasms with mediastinal nonseminomatous germ cell tumors, rather than with all germ cell tumors, remains unexplained.

In addition to hematologic neoplasia, several cases of idiopathic thrombocytopenia in association with mediastinal nonseminomatous germ cell tumors have been reported.^{56,57} These patients had normal numbers of megakaryocytes in the bone marrow; however, immune destruction of platelets could not be demonstrated. Prednisone and splenectomy were unsuccessful in increasing the platelet count; persistent thrombocytopenia caused significant morbidity in all patients and made treatment extremely difficult. At present, the cause of this syndrome is unknown.

A single case of mediastinal endodermal sinus tumor associated with the hemophagocytic syndrome has been reported.⁵⁸ In this patient, a proliferation of benign, mature macrophages with prominent hemophagocytosis was seen in the bone marrow. A partial tumor response was achieved with chemotherapy; however, the hemophagocytic syndrome persisted, and the patient subsequently died of progressive tumor.

PRETREATMENT EVALUATION AND STAGING The diagnosis of a mediastinal germ cell tumor should be considered in all young males with a mediastinal mass. In addition to physical examination and routine laboratory studies, initial evaluation should include CT of the chest and abdomen, and determination of serum levels of hCG and α -fetoprotein. Any symptoms suggestive of distant metastases should be appropriately evaluated with radiologic studies.

If distant metastasis or obviously unresectable intrathoracic tumor is present, a histologic diagnosis should be made using the least invasive approach, since surgical therapy does not play a role in the initial treatment of these patients, and rapid initiation of definitive systemic therapy is essential. In patients with tumors that seem localized to the mediastinum, exploration via thoracotomy or median sternotomy, with an attempt at tumor resection, is sometimes appropriate. Such an approach should not be used in patients with tumors that are obviously unresectable due to invasion of mediastinal structures or intrathoracic spread outside the anterior mediastinum. Surgical resection should also not be contemplated in patients with high levels of hCG or with any elevation of serum α -fetoprotein, since these patients have nonseminomatous tumors and should proceed immediately to definitive systemic therapy.

TREATMENT OF SEMINOMA Pure mediastinal seminomas are curable in the large majority of patients, even when metastatic at the time of diagnosis. These tumors are highly sensitive to radiation therapy and to combination chemotherapy, and selection of treatment therefore depends on disease stage and size of mediastinal tumor.

Approximately 20% of mediastinal seminomas are diagnosed after a chest radiograph reveals an asymptomatic anterior mediastinal mass. Some of these patients have relatively small tumors, and a complete surgical resection can be easily accomplished at the time of surgical biopsy for diagnosis. Although surgical resection alone is curative in some of these patients,⁵⁹⁻⁶¹ a course of postoperative radiation therapy to the mediastinum should always be administered in order to prevent local recurrence.

The large majority of patients with mediastinal seminoma (at least 80%) are not candidates for surgical resection due to the large size of the mediastinal primary tumor, or the presence of distant metastases. Pure mediastinal seminomas share the exquisite radiosensitivity of testicular seminoma, and primary radiotherapy is often curative in these tumors. Although most reported series are relatively small, approximately 60% of patients achieve long-term disease-free survival following mediastinal irradiation.^{28,60,62,63} Most treatment failures are due to the appearance of distant metastases, rather than inadequate local tumor control. Specific recommendations for radiation therapy dosage and technique are based on the much larger experience in the treatment of metastatic testicular seminoma. A dose of 3,500 to 5,000 cGy is recommended by most investigators. This dose should be delivered over 6 weeks by external beam megavoltage irradiation, to a shaped mediastinal field, including the bilateral supraclavicular areas.^{63,64} Routine irradiation of the retroperitoneum is not necessary. The benefit of surgical debulking prior to definitive radiation therapy is doubtful. Unless complete tumor resection can be accomplished, extensive mediastinal procedures should be avoided, since they delay the initiation of more effective treatment modalities.

Highly effective systemic combination chemotherapy now offers an additional option for the treatment of patients with perimedastinal seminoma. When used in advanced testicular seminoma, intensive cisplatin-based regimens are at least as active as they are against nonseminomatous germ cell tumors. Table 92.1^{28,32,65-70} summarizes the experience with modern cisplatin-based combination regimens in the treatment of pure mediastinal seminoma. Even with bulky local tumors and frequent metastatic disease, the large majority of patients were cured with systemic therapy. Chemotherapy is equally effective in pure mediastinal seminoma as it is in advanced testicular seminoma.

Although no large comparative studies exist, the majority of data now favor systemic chemotherapy versus radiation therapy for most patients with pure mediastinal seminoma. In one nonrandomized study comparing initial treatments, 5 of 9 patients treated with initial radiation therapy have remained disease free, compared with 10 of 11 of patients receiving initial chemotherapy.²⁸ These results, in conjunction with the cure rate of greater than 80% seen in modern treatment series provide convincing evidence of the superiority of systemic chemotherapy in this group of patients.

The patients with bulky seminoma at any site frequently have residual radiographic abnormalities after chemotherapy. In most patients, these masses represent dense scirrhous reactions rather than viable seminoma or benign teratoma.⁷¹⁻⁷³ Because of the dense fibrosis, retroperitoneal node desection in such patients is difficult, is frequently incomplete, and can be associated with high mortality. When residual lesions are less than 3 cm in maximum diameter, all investigators agree that patients should be monitored without repeat biopsy or intervention, since residual active tumor is rare. When residual masses were greater than 3 cm in diameter, investigators at Memorial Sloan-Kettering Cancer Center found viable seminoma in 5 of 20 patients undergoing resection of residual radiographic abnormalities.⁷⁴ Therefore, biopsy of large residual lesions should be considered, so that patients requiring further therapy can be promptly identified. If immediate biopsy is not performed, patients should be monitored very closely, with early biopsy of any enlarging mass on chest radiography or chest CT.

In summary, most patients with mediastinal seminoma can be cured with therapy, and all patients should be approached with this intent. Patients with small tumors (usually asymptomatic) that appear resectable should undergo thoracotomy and attempted complete resection. Radical debulking procedures for patients with larger tumors are not indicated. In the subset of patients who undergo complete excision, postoperative radiotherapy (4,000 to 4,500 cGy) is curative in almost all patients and is the treatment of choice. All other patients should receive initial cisplatin-based chemotherapy, unless they have a specific medical contraindication to such therapy. In such patients with localized tumors in the mediastinum, radiation therapy is an acceptable alternative. Optimal chemotherapy includes four courses of bleomycin, etoposide, and cisplatin, as is recommended for poor-prognosis testicular germ cell tumors.⁷⁵

TREATMENT OF NONSEMINOMATOUS TUMORS Prior to the development of effective cisplatin-based chemotherapy, no effective therapy was available for nonseminomatous mediastinal germ cell tumors. Local treatment modalities were ineffective, due to the high percentage of patients with metastatic disease and the relative radioresistance of these tumors. In a review of the literature in 1975, Cox found no reported survivors among 85 cases of mediastinal teratocarcinoma.⁷⁶

The use of intensive cisplatin-based chemotherapy developed for the treatment of advanced nonseminomatous testicular neoplasms has improved the previously dismal outlook in patients with mediastinal nonseminomatous germ cell tumors. Although overall cure rates remain lower than those achieved in the treatment of testicular cancer, a compilation of results from reported series containing 10 or more patients and using optimal chemotherapy indicates a 41% long-term survival rate (Table 92.2).^{32-34,36,47,66-68,70,77,78} The large bulk of most mediastinal germ cell tumors at the time of diagnosis contributes to these relatively poor results. Comparable long-term survival rates of 40 to 50% have been reported when testicular germ cell tumors with far advanced, bulky metastases are treated with similar cisplatin-based regimens.⁷⁹ However, recent reviews of survival and prognostic factors have suggested that inherent biologic differences between mediastinal and testicular germ

cell tumors may also play a role in determining the relatively low cure rate.⁸⁰

At present, treatments for nonseminomatous germ cell neoplasms should be similar, regardless of the specific histology involved. Early reports suggested that pure endodermal sinus tumor of the mediastinum was a histology associated with particularly poor prognosis.⁸¹ However, several more recent reports using modern cisplatin-based regimens have achieved results similar to those in other mediastinal nonseminomatous tumors.^{34,82} Pure choriocarcinoma of the mediastinum has also been considered by some to have a poor prognosis.³² The rarity of this histology makes definitive conclusions difficult; at present, however, there is no rationale for treating these patients differently from other patients with nonseminomatous mediastinal tumors.

The treatment for mediastinal nonseminomatous germ cell tumors should follow guidelines for poor-prognosis testicular cancer. Initial treatment with four courses of bleomycin, etoposide, and cisplatin is considered standard therapy.⁷⁵ As in the treatment of testicular cancer, administration of chemotherapy at full doses and on schedule is important in obtaining optimal results. Following the completion of therapy, patients should be restaged with repeat serum tumor markers and CT scans of the chest and abdomen.

Subsequent management is determined by the response to initial chemotherapy (Fig. 92.1). Patients with normal CT scans and tumor marker levels should receive no further therapy. Approximately 20% of these patients subsequently relapse, with almost all relapses occurring during the first 2 years after completion of therapy. Standard follow-up of these patients includes monthly physical examination, chest radiography, and serum tumor marker determinations during the first year, and similar evaluations every 2 months during the second year following therapy.

Patients with persistent elevations of either hCG or α -fetoprotein following completion of initial therapy have residual active carcinoma and a very poor prognosis. Salvage regimens, such as VIP (etoposide or vinblastine, ifosfamide, and cisplatin) have been effective second-line treatments in 20 to 30% of patients with refractory testicular cancer,⁸³ but results with this approach in mediastinal germ cell tumors have been very poor. Only 5 of 73 patients (7%) with refractory extragonadal germ cell tumors treated with a cisplatin-containing regimen at Indiana University between 1976 and 1993 were long-term survivors.⁸⁴ These poor results included patients with highly refractory tumors who received high-dose chemotherapy with autologous bone marrow support; none of 28 such patients remain disease-free. High-dose therapy used as initial salvage therapy (i.e., second-line therapy) may be more useful; in one report, 5 of 16 patients with extragonadal germ cell tumors had a complete response after second-line treatment with high-dose carboplatin, etoposide, and ifosfamide.⁸⁵ High-dose therapy as part of initial treatment is also being evaluated in patients with poor-prognosis germ cell tumors.

Surgical intervention is often necessary in patients who have residual mediastinal abnormalities and normal serum tumor markers fol-

lowing initial combination chemotherapy. In this setting, approximately 75% of patients have either nonviable tumor or benign teratoma, with no evidence of active malignancy. Patients with a large component of teratocarcinoma in the original biopsy are more likely to have residual benign teratoma. Unresected benign teratoma can cause further problems, either by slow local growth or by subsequent malignant degeneration; resection is, therefore, therapeutic. Since resection of necrotic tumor or fibrosis is not therapeutic, the proper timing of surgery following chemotherapy has been debated. In some patients, residual necrotic tumor continues to decrease in size for several months after completion of therapy. Follow-up with serial scans in such patients sometimes results in the avoidance of a major operative procedure. It is reasonable to delay resection for 2 to 3 months in patients with partial radiographic response, as long as serial tumor shrinkage is observed on follow-up radiographs. Tumors that fail to decrease in size should be resected.

Patients with no viable tumor found at the time of surgical resection have the same low risk for subsequent relapse as do patients achieving complete remission with chemotherapy alone. These patients should be monitored without further therapy. If viable carcinoma is completely resected, further chemotherapy should be administered. Although experience with this approach is limited in mediastinal germ cell tumors, approximately 70% of patients with testicular cancer have long-term survival if they receive two additional courses of the same combination regimen used for first-line treatment.⁸⁶

Although the prognosis for patients with nonseminomatous mediastinal germ cell tumors has been markedly improved by the development of cisplatin-containing chemotherapy regimens, approximately half of these patients still die of uncontrolled tumor. Patients who do not achieve complete remission with primary therapy have extremely poor prognoses and are candidates for investigational approaches. Early use of high-dose therapy is being investigated.^{85,87} Paclitaxel and gemcitabine are active agents in patients whose cancer is refractory to cisplatin and etoposide^{88,89} and may improve the efficacy of salvage regimens. Further improvements in therapy will probably parallel the development of increasingly effective treatment for patients with poor-prognosis testicular germ cell neoplasms.

POORLY DIFFERENTIATED CARCINOMA OF THE MEDIASTINUM

Occasionally, the biopsy diagnosis in a patient with a mediastinal tumor is "poorly differentiated carcinoma." This diagnosis poses difficult problems for the clinician, since it indicates a tumor with no histopathologic features specific enough to allow identification of the site of origin. Patients with poorly differentiated carcinoma in the mediastinum are sometimes assumed to have metastatic lung cancer with an undetectable primary lesion and are, therefore, assumed to be unresectable and incurable. In this setting, palliative radiation therapy is

Table 92.1. Mediastinal Seminoma: Treatment with Cisplatin-Based Combination Chemotherapy

Author, Year	Number of Patients	Received Previous Radiotherapy	Treatment Regimen	Number of Complete Responses (%)	Number of Long-Term Disease-Free Survivors (months)
Hainsworth, 198232	4	3	PVB	3 (75%)	3 (> 24 months)
Jain, 198428	11	0	VAB-6, 8, PVB 1, DDP/CTX 2	10 (91%)	10 (19 + 46 months)
Logothetis, 198534	4	Unspecified	DDP/CTX 3, CISCA21	4 (100%)	4 (unspecified)
Loehrer, 198765	9	7	PVB \pm A or BEP	8 (89%)	7 (unspecified)
Bukowski, 199366	8	0	PVB/EBAP	5 (63%)	4 (> 24 months)
Delgado, 199367	6	0	VAP-6, PVB, BEP	5 (83%)	5 (5–103 months)
Goss, 199468	8	0	BEP 6, BEP + RT 1, VAB-6 1	8 (100%)	8 (4–132 months)
Mencel, 199469	19	0	VAP-6, EP	19 (100%)	19 (> 24 months)
Gerl, 199670	4	1	VIOR, EIP	4 (100%)	4 (> 24 months)

DDP = cisplatin; A = Adriamycin; CTX = cyclophosphamide; PVB (Einhorn regimen) = cisplatin 20 mg/m² IV x 5 days, vinblastine 0.15 mg/kg D 1,2, bleomycin 30 units weekly, cycle repeated q 3 weeks; VAB-6 = multi-drug regimen developed at Sloan-Kettering; CISCA₂ = multidrug regimen developed at M.D. Anderson; BEP = bleomycin 30 units weekly, etoposide 100 mg/m² IV x 5 days, cisplatin 20 mg/m² IV x 5 days, cycles repeated q 3 weeks; EBAP = etoposide, bleomycin, cisplatin.

Table 92.2. Results of Initial Treatment with Cisplatin-Based Combination Chemotherapy in Nonseminomatous Mediastinal Germ Cell Tumors

Author, Year	Number of Evaluable Patients	Chemotherapy Regimen	Number of Complete Responders (%)	Number of Long-Term (> 24 months) Disease-Free Survivors (%)
Funes, 1981 ⁷⁷	13	PVB	6 (46%)	5 (38%)
Hainsworth, 1982 ³²	12	PVB ± A	7 (58%)	7 (58%)
Logothetis, 1985 ^{33,34}	11	CISCA II CISCA/VBIV	NA	4 (36%)
Israel, 1985 ³³	11 ^a	VAB-6	NA	4 (36%)
Kay, 1987 ³⁶	11	PVB, BEP	7 (64%)	5 (45%)
Nichols, 1990 ¹⁷	31	PVB ± A, BEP	18 (58%)	13 (42%)
Bukowski, 1993 ⁶⁶	16	PVB/EBAP	9 (56%)	9 (56%)
Delgado, 1993 ⁶⁷	40	VAB-6, PVB, BEP	15 (38%)	14 (35%)
Gerl, 1996 ⁷⁰	12	PVB, BEP, ECBC	8 (67%)	6 (50%)
Fizazi, 1998 ⁷⁸	29	VAP-6, PveVB, PVB, BEP	19 (60%)	10 (34%)
Total	186		89 (54%)	73 (39%)

PVB = cisplatin 20 mg/m² IV x 5 days, vinblastine 0.15 mg/kg D1, 2, bleomycin 30 units weekly; VAB-6 = multi-drug regimen developed at Sloan-Kettering; A = Adriamycin; CISCAII, CISCA/VBIV = multi-drug regimens developed at M.D. Anderson; BEP = bleomycin 30 units weekly, etoposide 100 mg/m² IV x 5 days, cisplatin 20 mg/m² IV x 5 days, cycles repeated q 3 weeks; EBAP = etoposide, bleomycin, doxorubicin, cisplatin; ECBC = etoposide, cisplatin, bleomycin, cyclophosphamide; PveVB = cisplatin, etoposide, vinblastine, bleomycin; NA = not available.

^aIncludes patients with retroperitoneal tumors.

often administered. However, this approach is no longer adequate, since further clinical and pathologic evaluation can establish a definitive diagnosis with specific therapeutic implications in some of these patients. In addition, some patients with poorly differentiated carcinoma involving the mediastinum are curable with intensive cisplatin-based chemotherapy.

A brief discussion of this important subset is also included here, however, since some poorly differentiated carcinomas of the mediastinum may be unrecognized or histologically atypical extragonadal germ cell tumors. All patients should have α -fetoprotein and hCG measured, as well as CT of the chest and abdomen. If other studies are nondiagnostic, most will require fiberoptic bronchoscopy.

PATHOLOGIC EVALUATION Critical pathologic evaluation of mediastinal tumors is essential, since a variety of neoplasms with specific therapeutic implications can arise in this location (e.g., mediastinal germ cell tumor, lymphoma, thymoma). In addition, effective therapy also exists for some neoplasms that commonly metastasize to the mediastinum

(e.g., small cell lung cancer). Following light microscopic examination of an adequate biopsy specimen, immunoperoxidase staining and electron microscopy are useful in distinguishing between the various neoplasms occurring in the mediastinum. Using these methods, lymphoma and neuroendocrine tumors (such as small cell lung cancer) can be reliably identified, and appropriate therapeutic approaches can be defined. Molecular genetic analysis should also be performed, if possible, since identification of an i(12p) chromosomal abnormality is diagnostic of a germ cell tumor.^{18,19}

DIAGNOSTIC EVALUATION AND STAGING WORKUP Patients with poorly differentiated carcinoma who have neuroendocrine features detected by either electron microscopy or immunoperoxidase staining are a distinct subset and require special evaluation and treatment. Small cell lung cancer should be suspected in patients with a smoking history, and fiberoptic bronchoscopy should be performed. In patients who are nonsmokers and who have no lung primary detected at bronchoscopy, the diagnosis of small cell lung cancer is unlikely. Multiple

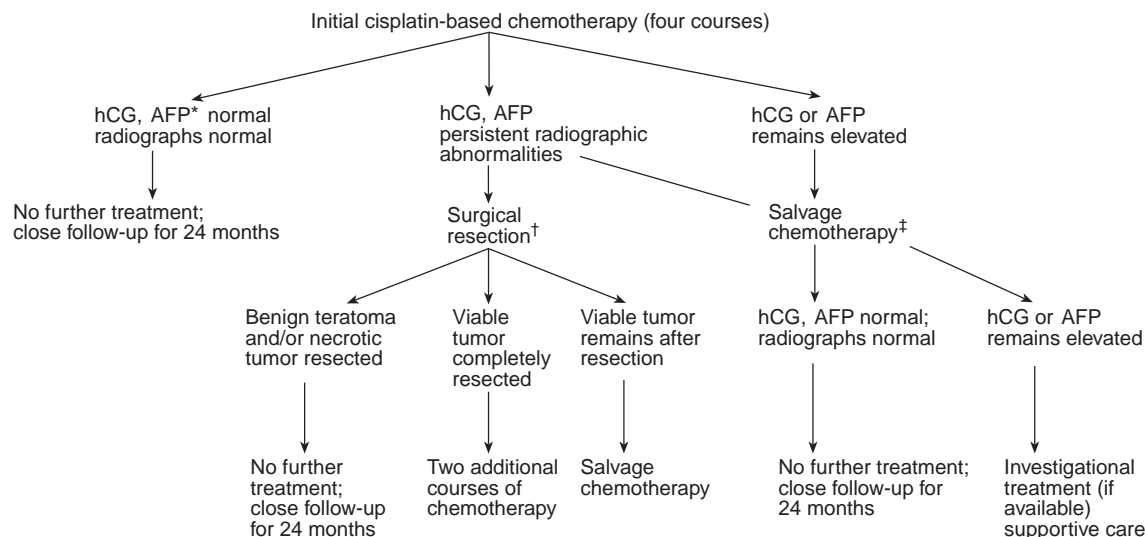


Figure 92.1. Management of nonseminomatous mediastinal germ cell tumors after completion of initial chemotherapy.

*AFP = α -fetoprotein.

† Timing of resection depends on tumor response, initial histology (see text).

‡ No standard salvage regimen established mediastinal germ cell tumors after completion of initial chemotherapy.

sites of metastasis are often detected when staging studies are performed; however, identification of a primary site is unlikely. Further staging evaluation is unlikely to define a primary site, however. Although the origin and biology of these neuroendocrine tumors are not well defined, they are usually responsive to treatment with platinum-based or paclitaxel-based chemotherapy, with a minority achieving complete response and long-term survival.⁹⁰

TREATMENT The diagnostic evaluation defines specific therapy for some patients in this group. Patients with elevated levels of either hCG or α -fetoprotein should be treated for a mediastinal nonseminomatous germ cell tumor, even if this diagnosis is not made by histologic examination. Patients who have an endobronchial lesion found at bronchoscopy probably have lung cancer; those with neuroendocrine features should receive therapy for small cell lung cancer, while those lacking these features should be treated for non-small cell lung cancer.

A few patients with poorly differentiated carcinoma have tumors that seem limited to the mediastinum and do not extensively invade local structures. In these patients, an attempt at total tumor resection should be considered, although this approach will be curative in only a small percentage.

Most patients in this group have obviously unresectable tumors and require other treatment modalities. A few such patients who were cured with cisplatin-based combination chemotherapy have been reported by several investigators.^{21,22} In a larger group of patients with unknown primary cancer, we treated 43 patients with poorly differentiated carcinoma or poorly differentiated adenocarcinoma located predominantly in the mediastinum.⁹¹ These patients represented 19% of our entire group of patients with poorly differentiated carcinoma of unknown primary site. The median age was 38 years; 32 patients had other metastatic sites in addition to the mediastinum. Only 5 of 43 patients (12%) had elevated serum levels of hCG or α -fetoprotein. All patients received cisplatin-based chemotherapy; 13 patients (30%) had complete response, and 7 patients (16%) are long-term disease-free survivors. Review of the light microscopic features in these patients failed to reveal any previously unsuspected germ cell tumors or lymphomas.

In summary, patients with mediastinal tumors initially diagnosed as poorly differentiated carcinoma are a heterogeneous group. Some of these patients actually have well-defined tumor types, which can be identified with additional pathologic or clinical evaluation. Patients in whom a specific tumor is identified should be treated according to standard guidelines for that tumor type. A trial of platinum-based chemotherapy should be given to patients in whom no well-defined tumor type is recognized. Some of these patients have highly responsive neoplasms, and a minority appear to be cured with this treatment.

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